Exhibit H

Neurodegenerative causes of death among retired National Football League players

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ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players.

Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained through 2007. For analysis purposes, players were placed into 2 strata based on characteristics of position played: nonspeed players (linemen) and speed players (all other positions except punter/kicker). External comparisons with the US population used standardized mortality ratios (SMRs); internal comparisons between speed and nonspeed player positions used standardized rate ratios (SRRs).

Results: Overall player mortality compared with that of the US population was reduced (SMR 0.53, 95% confidence interval [CI] 0.48−0.59). Neurodegenerative mortality was increased using both underlying cause of death rate files (SMR 2.83, 95% CI 1.36−5.21) and multiple cause of death (MCOD) rate files (SMR 3.26, 95% CI 1.90−5.22). Of the neurodegenerative causes, results were elevated (using MCOD rates) for both ALS (SMR 4.31, 95% CI 1.73−8.87) and AD (SMR 3.86, 95% CI 1.55−7.95). In internal analysis (using MCOD rates), higher neurodegenerative mortality was observed among players in speed positions compared with players in nonspeed positions (SRR 3.29, 95% CI 0.92−11.7).

Conclusions: The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players. *Neurology*® 2012;79:1–1

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **CI** = confidence interval; **CTE** = chronic traumatic encephalopathy; **ICD** = International Classification of Diseases; **MCOD** = multiple cause of death; **NDI** = National Death Index; **NFL** = National Football League; **NIOSH** = National Institute for Occupational Safety and Health; **PD** = Parkinson disease; **SMR** = standardized mortality ratio; **SSR** = standardized rate ratio.

In 1994, the National Institute for Occupational Safety and Health (NIOSH) conducted a mortality study of National Football League (NFL) players.[1] One notable result was an increase in "nervous system" deaths due to 4 cases of amyotrophic lateral sclerosis (ALS). Little additional study on neurologic disorders in football players was conducted until several prominent NFL players retired from the game with lingering and unresolved neurologic sequelae from recurrent mild traumatic brain injuries (concussions).[2] Since then multiple studies have raised concerns about the longer-term health effects of recurrent concussions.[3,4] Research based on autopsy data has identified chronic traumatic encephalopathy (CTE) as a pathologically distinct neurodegenerative condition affecting a wide range of individuals, including football players, who have experienced multiple concussions.[5–7] CTE results from the progressive decline in neuron functioning occurring years or

decades after exposure to repetitive concussive injuries and presents clinically as progressive neurologic dysfunction affecting mental status, balance, and movement.[8]

The purpose of this article is to report the results of an analysis of NFL player mortality from neurodegenerative disorders including Alzheimer disease (AD), Parkinson disease (PD), and ALS. It is not possible to directly examine mortality from CTE because the pathologic refinement of the CTE diagnosis has only occurred within the last few years, and CTE is not listed as a cause of death in any revision of the International Classification of Diseases (ICD). As an alternative, because it is now known that neurologic conditions previously attributed to AD, PD, and ALS may actually have been related to CTE,[4,9] an analysis that combined all neurodegenerative causes of death was conducted; this analysis included deaths that may be related to CTE even if not reported as such on death certificates.

METHODS Full details of the cohort have been described previously.[1,10] In brief, the cohort includes 3,439 NFL players identified by a pension fund database of vested players with at least 5 credited playing seasons between 1959 and 1988. Vital status was ascertained from pension fund records, the Social Security Administration, and the Internal Revenue Service. Players were matched to the National Death Index (NDI) beginning in 1979 (when the NDI began) with follow-up through 2007. The NDI provided underlying and contributing causes of death, coded to the ICD revision in effect at the time of death. Death certificates were obtained from state vital statistics offices and were coded by a certified nosologist when death information was not provided by the NDI.

Mortality was analyzed using the NIOSH life table analysis system (LTAS.NET).[11] Analyses used US male mortality rates (1960−2007) for 119 cause of death categories.[12] Mortality for 3 neurodegenerative causes of death was evaluated using updated custom rate files.[13] Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were adjusted for race, age (in 5-year categories), and calendar year (in 5-year categories). Because AD and PD are more likely to be listed as a contributing cause than as the underlying cause, additional analyses used multiple cause of death (MCOD) rate files to examine all causes listed on the death certificates. Good candidates for MCOD analyses are diseases of long duration, not necessarily fatal, that are serious enough to be noted on the death certificate.[14]

Recent studies suggested that football players who play certain positions are at higher risk of concussion because of the high acceleration, rotational acceleration, and multiple impacts they experience during games.[15,16] Data collected using exposure assessment methods including video analysis, simulation and reconstruction techniques, and helmet-mounted accelerometers suggest that although linemen experience the highest number of head impacts, other positions experience higher acceleration impacts that result in concussions.[16–18] To examine possible neuro-

logic mortality differences from the high acceleration head impacts, we stratified the players into 2 categories based on position played[10] (identified using annual data compiled in commercial publications): speed (quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker) and nonspeed (all defensive and offensive linemen); punters and kickers were excluded from the stratified analysis. LTAS.NET was used to calculate directly standardized rate ratios (SRRs) and 95% CIs for the neurodegenerative causes using the nonspeed players as an internal referent; 95% CIs that excluded unity were considered to be statistically significant.

Standard protocol approvals, registrations, and patient consents. The protocol for this study was approved by the NIOSH Institutional Review Board and has been assigned approval number HSRB 06-DSHEFS-04XP.

RESULTS Approximately 39% of the cohort is African American, and 62% played speed positions (table 1). African American players comprise almost half (48%) of the speed stratum but only 28% of the nonspeed stratum. There were minimal differences between the strata for all other cohort characteristics. The cohort is relatively young (median age of 57 at date last observed), and only 10% are deceased.

Compared with that of US men, the overall mortality in the cohort was significantly reduced (table 2); however, mortality was significantly elevated for all neurodegenerative causes combined and for the subclassifications of AD (when all causes on death certificates were considered) and ALS. Mortality from PD was elevated but did not reach statistical significance. Overall, results based on all contributing causes were similar to results based on underlying causes with the exception of AD, which was more likely to be listed as a contributing cause rather than the underlying cause on death certificates. Neurodegenerative mortality stratified by speed position considered all death certificate causes (table 3). Compared with those for US men, SMRs for the speed positions were significantly elevated for all neurodegenerative causes combined, AD, and ALS, but not for PD. Neurodegenerative mortality was not elevated for the nonspeed positions. Compared with the nonspeed positions, mortality was nonsignificantly elevated for the speed positions for all neurodegenerative causes combined, AD, and ALS, but not for PD. These results were highly imprecise because of the small numbers.

DISCUSSION Although the overall mortality of this cohort is significantly lower than expected (SMR 0.53), the neurodegenerative mortality is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an in-

Table 1	Characteristics of the National Football League Players Cohort, overall and by position category (1960–2007)[a]		
Characteristic	Overall (n = 3,439)	Speed (n = 2,145)	Nonspeed (n = 1,166)
Race, n (%)			
White	2,070 (60)[b]	1,111 (52)	835 (72)
African American	1,355 (39)	1,029 (48)	323 (28)
Other	14 (<1)	5 (<1)	8 (1)
Vital status as of December 31, 2007, n (%)			
Alive	3,105 (90)	1,972 (92)	1,014 (87)
Dead	334 (10)	173 (8)	152 (13)
First credited season			
Median (range)	1973 (1950-1984)	1974 (1950-1984)	1972 (1950-1984)
<1980, n (%)	2,685 (78)	1,654 (77)	930 (80)
≥1980, n (%)	754 (22)	491 (23)	236 (20)
No. credited seasons (as of 1988/1989 season), median (range)[c]	8 (5-25)	7 (5-21)	8 (5-20)
Age at death, y, median (range)	54 (27-81)	54 (27-80)	53 (29-81)
Age at date last observed, alive			
Median (range)	57 (45-88)	56 (45-82)	57 (45-83)
<50 y, n (%)	633 (20)	409 (21)	203 (20)
50–54 y, n (%)	738 (24)	502 (25)	208 (21)
55–59 y, n (%)	565 (18)	338 (17)	206 (20)
60–69 y, n (%)	890 (29)	552 (28)	300 (30)
≥70 y, n (%)	279 (9)	171 (9)	97 (10)

[a] Player position was collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive end/lineman/tackle, guard, nose guard, tackle, center, and offensive end/guard/lineman/tackle). Punters and kickers are included in the overall results only.
[b] Percentages may not sum to 100% due to rounding.
[c] Number of credited seasons does not necessarily equal the number of seasons played.

creased risk of neurodegenerative disease among football players.

It is not possible to determine from our study what has caused this increased risk. Research suggests that football players who have experienced one or more concussive blows to the head are at increased risk of neurologic disorders. In retired professional players, one study observed a 5-fold prevalence of mild cognitive disorders and a 3-fold prevalence of significant memory problems for players who experienced 3 or more concussions compared with players with fewer than 3 concussions.[3] Excess neurologic mortality and morbidity has also been reported in players of other sports for which head impacts and concussion are common: soccer, boxing, horse racing, and hockey.[19]

Studies that examined the incidence of concussion in football players found that players in speed positions experienced concussions more commonly than players in nonspeed positions. Speed players are those who are able to build up considerable momentum before the point of being tackled or tackling another player.[15,17,20] Offensive and defensive linemen (nonspeed players)

usually engage other players soon after the football is snapped, thus mitigating the potential to build up momentum before a tackle or a block.[15,16]

Although our study used causes of death from AD, PD, and ALS as reported on death certificates, recent research now suggests that CTE may have been the true primary or secondary factor in some of these deaths. Whereas CTE is a clinically distinct neurologic diagnosis, CTE symptoms are often similar to those found in patients with AD, PD, and ALS.[6,21] In addition, CTE is not listed as a distinct cause of death recognized in current or previous ICD revisions, precluding the calculation of CTE-specific results. To account for possible misclassification, we reported combined results for all neurodegenerative causes.

Our study had several limitations. Our analysis is based on a few neurodegenerative deaths; therefore, the confidence intervals surrounding our SMR and SRR values are relatively broad. The few deaths also limited our ability to stratify players into more than 2 broad position categories; therefore, we were not able to identify potentially important differences in neu-

Table 2	Overall mortality, selected causes, National Football League Players Cohort (1960−2007)				
	Underlying[a]			Contributing[b]	
Cause of death	No.	SMR (95% CI)		No.	SMR (95% CI)
All deaths	334	0.53 (0.48-0.59)		782	0.54 (0.51-0.58)
All cancers	85	0.58 (0.46-0.72)		122	0.63 (0.53-0.76)
All cardiovascular diseases	126	0.68 (0.56-0.81)		340	0.71 (0.64-0.79)
All neurodegenerative causes	10	2.83 (1.36-5.21)		17	3.26 (1.90-5.22)
Dementia/Alzheimer disease[c]	2	1.80 (0.22-6.50)		7	3.86 (1.55-7.95)
Amyotrophic lateral sclerosis[d]	6	4.04 (1.48-8.79)		7	4.31 (1.73-8.87)
Parkinson disease[e]	2	2.14 (0.26-7.75)		3	1.69 (0.35-4.94)
All injuries	41	0.63 (0.45-0.86)		57	0.69 (0.52-0.89)
Violence	13	0.27 (0.14-0.46)		13	0.26 (0.14-0.45)
All other causes	59	0.34 (0.26-0.43)		233	0.37 (0.33-0.42)

Abbreviations: CI = confidence interval; ICD = International Classification of Diseases; SMR = standardized mortality ratio (US referent rates).

[a] Underlying indicates the number of deaths for which the cause was selected as the underlying cause of death on the death certificate.

[b] Contributing indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing).

[c] ICD-7 codes 304−305, ICD-8 codes 290.0−290.1, ICD-9 codes 290.0−290.3 and 331.0, and ICD-10 code G30; includes senile and presenile dementia but excludes cerebrovascular dementia because it is probably due to underlying cerebral vascular disease.

[d] ICD-7 code 356.1, ICD-8 code 348.0, ICD-9 code 335.2, and ICD-10 code G12.2.

[e] ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, and ICD-10 codes G20−G21.

rodegenerative mortality risk across the various positions included within the speed position group.

Because our cohort was limited to longer-term professional players, our findings may not be applicable to other professional or nonprofessional football players. However, recent autopsy studies have reported pathologic findings of CTE in college-age and professional football players with relatively short playing careers.[22] We did not have data on player injuries or concussions. If chronic mild to moderate concussion is an actual risk factor for neurodegenerative mortality, the magnitude of the risk may depend on the intensity and frequency of brain injuries incurred over a number of years. A few studies have attempted to measure these injuries for a limited number of players over a limited period of time but such measurements have proven to be difficult and underreporting is a problem.[23,24] Finally, we did not have information on environmental, genetic, or other risk factors for neurologic disorders.

Although the results of our study do not establish a cause-effect relationship between football-related concussion and death from neurodegenerative disorders, they do provide additional support for the find-

Table 3	Mortality for neurodegenerative causes of death (considering all causes of death reported on the death certificate) stratified by position category, National Football League Players Cohort (1960−2007)				
	Nonspeed[a]		Speed		Speed vs nonspeed: SRR (95% CI)
Cause of death	No.[b]	SMR (95% CI)	No.	SMR (95% CI)	
All neurodegenerative causes	3	1.58 (0.33-4.61)	14	4.74 (2.59-7.95)	3.29 (0.92-11.7)
Dementia/Alzheimer disease[c]	1	1.51 (0.04-8.41)	6	6.02 (2.21-13.1)	5.96 (0.72-49.6)
Amyotrophic lateral sclerosis	1	1.71 (0.04-9.50)	6	6.24 (2.29-13.6)	3.88 (0.47-32.2)
Parkinson disease	1	1.53 (0.04-8.53)	2	2.01 (0.24-7.25)	1.19 (0.11-13.2)

Abbreviations: CI = confidence interval; SMR = standardized mortality ratio (US multiple cause of death referent rates); SRR = directly standardized rate ratio (internal analysis).

[a] Punters and kickers were excluded, and remaining player positions were collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive and offensive linemen).

[b] Number indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing causes).

[c] Includes senile and presenile dementia but excludes cerebrovascular dementia.

ing that professional football players are at an increased risk of death from neurodegenerative causes. Additional studies to quantify the cumulative effects of brain injuries, in particular the relative effects of concussive-level injuries, will be of particular importance in understanding the underlying disease mechanisms.

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